An IFN-Associated Cytotoxic Cellular Immune Response against Viral, Self-, or Tumor Antigens Is a Common Pathogenetic Feature in "Interface Dermatitis"

Joerg Wenzel[1] and Thomas Tüting[1]

The term "interface dermatitis" (ID) involves a specific histological inflammatory pattern that is characterized by a cytotoxic lymphocytic infiltration and a hydropic degeneration of the basal epidermal layer. ID is typically seen in autoimmune skin disorders such as lichen planus (LP), cutaneous lupus erythematosus (CLE), and may also appear during immune reactions against drugs, viruses, and tumors. Recent studies have shown that the type-I IFN system is involved in cutaneous autoimmune diseases characterized by ID. IFNs induce the expression of proinflammatory cytokines and chemokines, which support the cellular immune response. The role of IFNs in ID is supported by a close morphological association between the expression pattern of IFN-inducible proteins and the distribution of CXCR3+ lymphocytes. The IFN-inducible chemokine CXCL10 is expressed in exactly those areas where cytotoxic lymphocytes invade the basal epidermis and cause keratinocyte death. A similar picture can be found in early herpes simplex viral skin lesions and viral warts, but also in "lichenoid" actinic keratosis and invasive squamous cell carcinoma. These data suggest that ID morphologically reflects a common IFN-driven cytotoxic attack affecting the basal keratinocytes under different conditions, which is important for antiviral and antitumor immune response, but is inappropriately activated in autoimmune skin disorders.

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Abbreviations: AK, actinic keratosis; CLE, cutaneous lupus erythematosus; CTL, cytotoxic T-lymphocyte; HSV, herpes simplex virus; ID, interface dermatitis; IRF, IFN-regulatory factor; LP, lichen planus; MxA, myxovirus A protein; PRR, pattern-recognition receptor; SCC, squamous cell carcinoma; SLE, systemic lupus erythematosus; TLR, Toll-like-receptor

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THE TYPE-I IFN SYSTEM IS ACTIVATED IN SKIN DISEASES WITH AN ID

"Interface dermatitis" (ID) is a specific histomorphological pattern of the basal epidermal layer, which is characterized by vacuolar changes (liquefaction), appearance of apoptotic keratinocytes (Civatte bodies), and infiltration of CD8+ lymphocytes. Additionally, an upper dermal infiltrate of varying intensity is typically seen (Patterson, 1991; LeBoit, 1993). Many skin diseases may manifest with an ID, including autoimmune skin disorders (lichen planus (LP), cutaneous lupus erythematosus (CLE), dermatomyositis, lichen sclerosus), and immune reactions against drugs (drug eruption, toxic epidermal necrolysis), viruses (erythema multiforme, herpes simplex virus (HSV) infection, viral warts), and tumors ("lichenoid" actinic keratosis (LAK)) (Patterson, 1991; LeBoit, 1993). Lists of morphological "look-alikes" often provide insights into similar pathophysiologies of disease processes. It had previously been suggested that an antigen-specific, cell-mediated cytotoxic immune reaction against basal keratinocytes might be the common feature of ID (LeBoit, 1993).

During the last years it became evident that activation of the type-I IFN system is involved in many skin-diseases characterized by ID. Initially, Fah *et al.* reported in 1995 that high amounts of the antiviral myxovirus A protein (MxA) can be found not only in acute viral skin lesions (chickenpox, herpes zoster, herpes simplex), but also in autoimmune conditions like lupus erythematosus and LP. The MxA protein is strongly induced by type-I IFNs (IFN-α/β), whereas other cytokines (including IFN-γ) are poor inducers. These observations indicated an activation of the type-I IFN system in these autoimmune skin disorders (Fah *et al.*, 1995). Recent molecular insights supported the view that the type-I IFN system not only participates in antiviral and antitumor immune defense, but also plays an important pathophysiological role in autoimmune diseases that are characterized by an ID-pattern, including LP, lupus erythematosus, and dermatomyositis (Greenberg *et al.*, 2005; Ronnblom *et al.*, 2006; Wenzel *et al.*, 2007a, c).

TYPE-I IFN-ASSOCIATED INFLAMMATION IN LP

LP is regarded as the prototype autoimmune skin disorder with "lichenoid" ID (Patterson, 1991; LeBoit, 1993). As shown in Figure 1, the typical histological findings include a basal hydropic degeneration of the epidermis, formation of Civatte bodies, and a band-like lichenoid lymphocytic

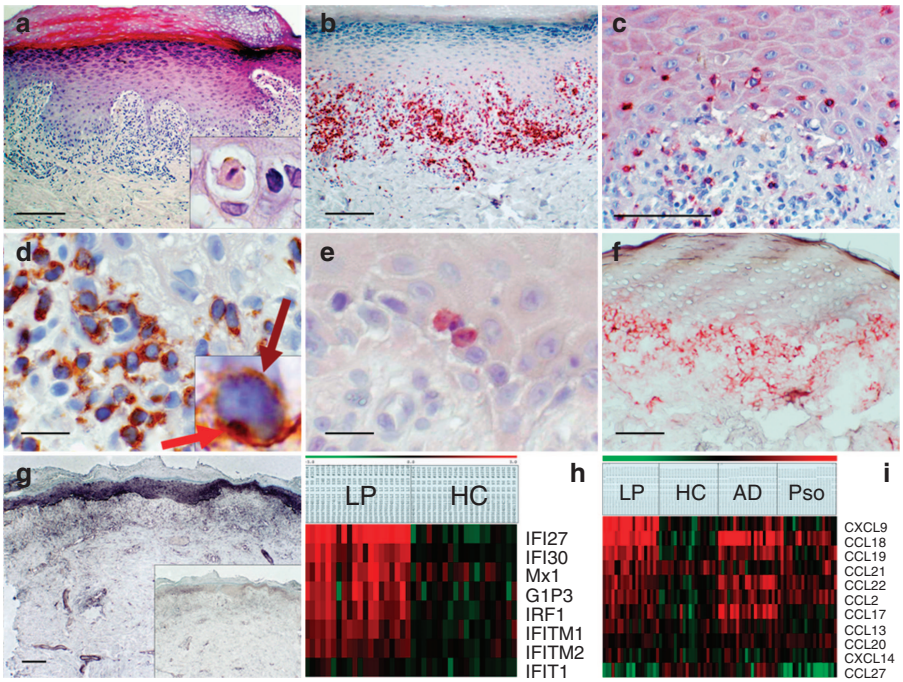

Figure 1. ID in LP. LP is the prototype cell-rich ID. It presents histologically with the typical band-like ''lichenoid'' inflammatory infiltrate, vacuolization of the basal layer, hyperkeratosis, hypergranulosis, and ''sawtooth-like'' acanthosis. Some Civatte bodies are found (**a**, H&E). CD3+ T cells dominate the inflammatory infiltrate (**b**). CD8+ lymphocytes invade the basal epidermis (**c**). Large numbers of CXCR3 cytotoxic effector lymphocytes are found at the dermo-epidermal junction and in the upper dermis (**d**, CXCR3: brown; granzyme B, red). Keratinocytes undergo apoptosis in exactly those areas where lymphocytes infiltrate the epithelium (**e**, caspase 3). Large numbers of ''natural IFN-producing'' CD123+ pDCs are found within the band-like infiltrate (**f**). *In situ* hybridization demonstrates strong IFN-α mRNA expression within the epidermis and the upper dermis (**g**). The role of type-I IFN production is supported by detection of several IFN-regulated genes in gene-expression analyses of lesional LP-skin biopsies (**h**). The IFN-inducible chemokine CXCL9, which is a ligand for CXCR3, was the best marker to distinguish LP from other inflammatory skin disorders such as atopic dermatitis (AD) and psoriasis (Pso). Bar = 100 μm (**a**, **b**, **c**, **f**, **g**) or 500 μm (**d**, **e**). Expression ratio (**h**, **i**) ranges from threefold downregulated (green) to threefold upregulated (red). Abbreviations: H&E, hematoxylin–eosin; HC, healthy control.

infiltrate in the upper dermis, which is dominated by T cells. It has been suggested that autoreactive CD8+ T cells recognizing epithelial antigens are involved in the pathogenesis of LP (Sugerman *et al.*, 2000; Santoro *et al.*, 2004). First evidence for a role of type-I IFNs in LP came from clinical observations of an exacerbation of this disease after therapeutical application of recombinant IFN-α (Herrera Saval and Camacho Martinez, 1999; Pinto *et al.*, 2003). Large numbers of plasmacytoid dendritic cells (pDCs) are detectable in LP skin lesions and may be an important source of lesional type-I IFN production in LP (Figure 1; Santoro *et al.*, 2005; Wenzel *et al.*, 2006a). Suomela *et al.* (2004) found strong mRNA expression for the IFNα-inducible proteins MxA and IFI27 in LP skin lesions, which agreed largely with immunohistological studies revealing strong MxA expression on the protein level (Fah *et al.*, 1995; Wenzel *et al.*, 2006a). *In situ* hybridization analyses detected IFN-α mRNA in the epidermis and within the inflammatory infiltrate (Figure 1g; Wenzel *et al.*, 2007a).

The interaction between the IFN-inducible chemokines, CXCL9 and CXCL10, and their common receptor, CXCR3, appears to play a central role in the development of the typical ID pattern. Both chemokines are strongly expressed in LP skin lesions, as demonstrated by several *in situ* hybridization and PCR analyses (Spandau *et al.*, 1998; Tensen *et al.*, 1999; Ichimura *et al.*, 2006). In a recent global gene-expression profiling analysis, we were able to show that CXCL9 is the best marker to distinguish LP from other inflammatory skin disorders such as atopic dermatitis and psoriasis (Wenzel *et al.*, 2007a). Importantly, several IFN-regulated genes, including Mx1, IFI27, IFI30, G1P3, IFN-regulatory factor-1 (IRF-1), IFITM1, and IFITM2, were strongly induced in LP, supporting the involvement of the IFN system in this disease (Figure 1h and i).

Immunohistological analyses confirmed strong expression of the CXCR3 ligands in LP on the protein level. CXCL9 was found in the whole epidermis, whereas CXCL10 was predominantly expressed in the hydropically degenerated basal epidermal areas (Wenzel *et al.*, 2006a, 2007a). Here, cytotoxic CXCR3+ lymphocytes invade the epidermis and induce keratinocytic apoptosis (Figure 1d and e). Interestingly, CXCL10 is also found within the cytolytic granules of infiltrating lymphocytes in LP. Its release along with the cytotoxic proteins at the dermo-epidermal junction probably represents an important self-recruiting mechanism for CXCR3+ effector cells and might be involved in the chronic interface inflammation typically seen in LP (Iijima *et al.*, 2003).

ROLE OF THE TYPE-I IFN SYSTEM IN ANTIVIRAL IMMUNITY

From an evolutionary point of view, the type-I IFN system most likely has a pivotal role in antiviral defense, including coordination of the antiviral cellular immunity (Stetson and Medzhitov, 2006). This became particularly clear when mice lacking the IFN-α/β receptor died rapidly after dengue virus infection (Shresta *et al.*, 2004). How cells recognize the presence of virus on the molecular and cellular level remained unclear until recently. Now it has become evident that viral nucleic acids are sensed by germline-encoded pattern-recognition receptors (PRRs) (Akira *et al.*, 2006). Two complementary PRR systems account for most virus detection (Stetson and Medzhitov, 2006). One class of PRRs, the Toll-like-receptors (TLRs), are expressed on the cell surface and in the endosomes of specialized immune cells such as pDCs. TLR3 recognizes viral double-stranded DNA, TLR7 and 8 bind viral ssRNA, and TLR9 binds bacterial or viral double-stranded DNA with CpG motifs (Kawai and Akira, 2006). Different adaptor molecules link the endosomal viral recognition via TLRs with IFN-gene expression. TLRs7–9 use MyD88 for intracellular signal transduction. TLR3 uses Toll/IL-1-receptor domain-containing adaptor inducing IFN-β (TRIF) as an adaptor. Further downstream adaptor molecules, including IRFs 3, 5, and 7, are needed to induce the expression of type-I IFNs and other proinflammatory proteins (Ronnblom *et al.*, 2006).

The other class of PRRs, exemplified by the helicases MDA5 and RIG-I, are expressed in the cytosol of most cells. MDA5 binds viral dsRNA, RIG-I senses 3P-RNA, and the recently identified DNA-receptor (DAI) recognizes viral ssDNA (Akira *et al.*, 2006; Stetson and Medzhitov, 2006; Unterholzner and Bowie, 2008). These receptors induce IFN expression via IFN-β-promoter stimulator 1 (IPS-1) (also known as MAVS, VISA, or CARDIF). IPS-1 in turn triggers signaling pathways, including activation of the protein kinases TBK1 and IKKε, responsible for the phosphorylation of IRF3, a key transcription factor involved in type-I IFN synthesis (Vitour and Meurs, 2007).

Type-I IFNs induce several direct antiviral mechanisms. IFN-induced proteins block viral replication, counteract cell proliferation, and trigger apoptotic pathways in infected human cells. Additionally, type-I IFNs bridge the innate and adaptive immune system. They are able to activate DCs, stimulate DC maturation, enhance cross-presentation and T-cell-survival, and support subsequently the expression of proinflammatory cytokines (Maher *et al.*, 2007). IFN-inducible chemokines play a central role in the recruitment of effector immune cells into the skin (Stanford and Issekutz, 2003). Here, interactions between the chemokine receptor CXCR3, which is expressed on pDCs, Th1-cells, and CD8+ effector T-lymphocytes, and its IFN-inducible ligands, the chemokines CXCL9 (MIG), CXCL10 (IP10), and CXCL11 (I-TAC) are important (Liu *et al.*, 2005). A model of viral IFN induction is given in Figure 2.

During viral infection of the epidermis, for example with HSV or in verruca vulgaris (VV), cutaneous DCs become activated by the initial innate immune response, migrate to

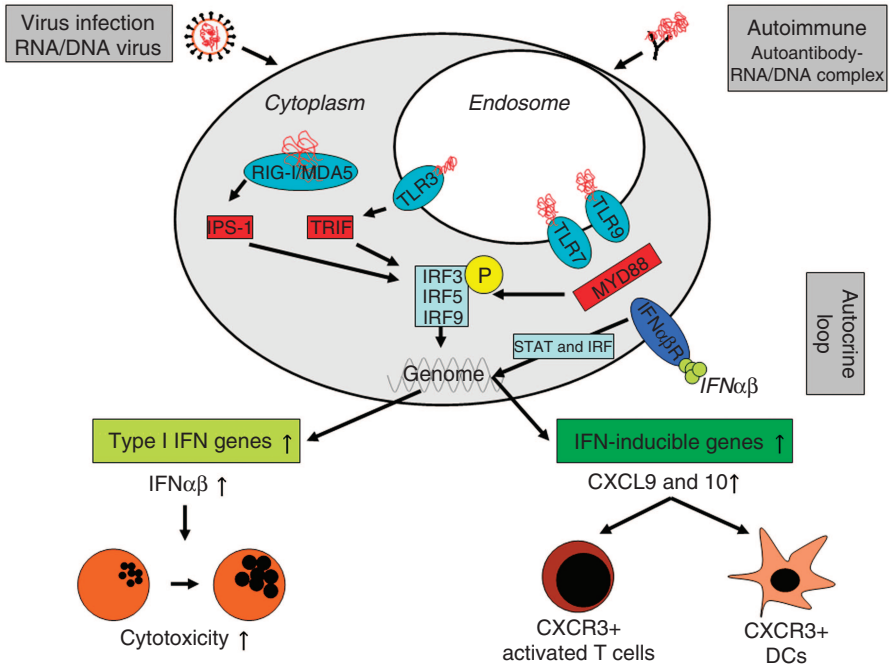

Figure 2. Mechanisms of IFN induction in viral infection and autoimmune disease. Viral infections are sensed by two complementary systems of PRRs, which recognize viral nucleic acids. One class of PRRs, the TLRs (TLRs 3, 7, 9), is expressed in the endosomes of specialized immune cells. The other class, here exemplified by the helicases RIG-I and MDA5, is expressed in the cytosol of most cells. The PRRs use different adaptor molecules (Myd88, TRIF, IPS1) to activate IRFs that induce expression of type-I IFNs. An autocrine loop via the IFN-αβ receptor is important for the expression of IFN-inducible proteins (for a detailed review, see Akira *et al.*, 2006). Importantly, recent studies indicated that the IFN system is also involved in autoimmune disorders such as SLE. Here, immune complexes comprising autoantibodies and endogenous RNA/DNA have been shown to trigger TLR7 or TLR9 (reviewed by Ronnblom *et al.*, 2006).

the regional lymph node, and mediate T-cell priming (Yoneyama *et al.*, 2005; Wuest *et al.*, 2006). Intact TLR9- and type-I IFN-signaling pathways are required to augment HSV-1-induced chemokines CXCL9 and CXCL10 (Wuest *et al.*, 2006). The interaction between these CXCL chemokines and their receptor, CXCR3, plays an important role in the recruitment of anti-HSV-specific cytotoxic T-lymphocytes (CTLs) into the target tissue (Lundberg and Cantin, 2003). T-lymphocytes capable of IFN-γ secretion and HSV-specific cytolysis have been isolated from human herpetic lesions. The subsequent resolution of HSV lesions is associated with the detection of HSV-specific cytolytic CD8+ T-lymphocyte activity, and requires IFN-γ and either perforin- or Fas-mediated cytolytic mechanisms (Dobbs *et al.*, 2005). This antiviral immune response represents a typical mechanism of antigen-specific cytotoxic immunity leading to destruction of virus-infected epidermal cells. Importantly, an ID pattern with vacuolar degeneration along the basal layer and Civatte bodies is often seen in early HSV skin lesions. Older lesions show typical acantholytic, intra-epidermal vesicles (Huff *et al.*, 1981; Sumegi, 1982; Patterson, 1991). A T-lymphocytic lichenoid inflammation with an ID pattern is also regularly seen in VV (Kossard *et al.*, 1980; Figure 3). Typical immunohistological findings demonstrating the expression pattern of an IFN-associated immune response in VV, are depicted in Figure 4; MxA and CXCL9 are strongly expressed within the whole epidermis, whereas CXCL10 is found in exactly those areas where CXCR3+ CTL invade the basal epidermal layer.

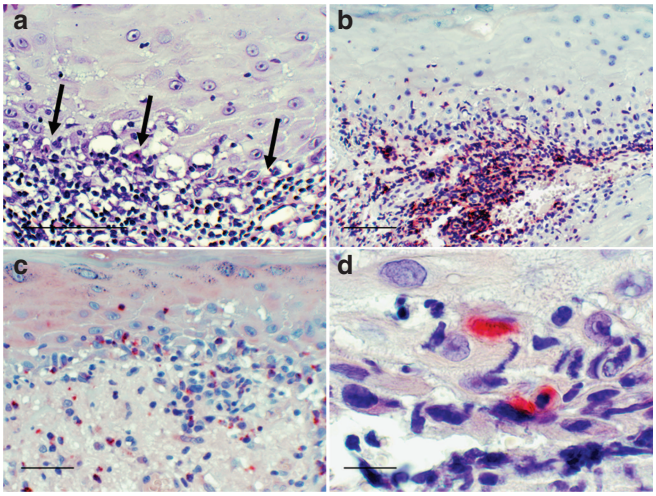

Figure 3. ID in viral skin disorders. Antigen-specific T cells recognizing viral antigens presented by infected keratinocytes are a hallmark of viral skin infections by HSV or human papillomavirus. As shown in this figure, the cytotoxic immune response may manifest with an ID pattern. Depicted are the histological pictures of a VV biopsy. A dense lichenoid inflammatory infiltrate that invades the basal epidermal layers is found in the upper dermis. A hydropic degeneration with several Civatte bodies (arrows) is found in the epithelium (**a**, hematoxylin–eosin). CD3+ T lymphocytes dominate the inflammatory infiltrate (**b**). Numerous cells express cytotoxic markers such as Tia1 (**c**). In those skin areas where the effector lymphocytes invade the epithelium, keratinocytes undergo apoptosis (**d**, demonstrated by caspase 3 staining). Bar = 100 μm (**a**–**c**) or 500 μm (**d**).

THE TYPE-I IFN SYSTEM IN LUPUS ERYTHEMATOSUS

Clinical observations suggested that type-I IFNs are also involved in the pathogenesis of systemic lupus erythematosus (SLE) for more than 20 years. Patients with acute SLE often present with flu-like symptoms such as fever, fatigue, and rash, which reflect high serum levels of type-I IFN, and correlate with both disease activity and severity (Hooks *et al.*, 1981; Dall'era *et al.*, 2005). Direct evidence for a role of type-I IFNs in SLE came from clinical observations of SLE exacerbation after treatment with recombinant IFN-α (Ronnblom *et al.*, 1991). These findings were supported by results from several experimental mouse models. IFN injection into NZB/W mice induced severe autoimmune glomerulonephritis accompanied by increased titers of serum anti-ssDNA and deceased survival (Adam *et al.*, 1980). Treatment of autoimmune lupus NZB x NZWF1 (B/WF1) mice with IFN-releasing agents increased the titer of anti-nuclear antibodies and the severity of glomerulonephritis (Hasegawa and Hayashi, 2003). Moreover, introducing a null mutation for the IFN-receptor gene into the autoimmune lpr mice clearly reduces lupus-like disease (Braun *et al.*, 2003; Santiago-Raber *et al.*, 2003). In humans, polymorphisms of IFN-related genes were recently found to be associated with an increased susceptibility for the development of SLE (Graham *et al.*, 2006).

Enhanced serum levels of IFN-α in SLE patients had already been detected during the 1980s, but the source of IFN remained unclear (Hooks *et al.*, 1981). In 1999, Vallin *et al.* (1999) observed that DNA-containing immune complexes of SLE patients induced IFN-α production by pDCs. The occurrence of these ''interferonic'' immune complexes is associated with active disease (Vallin *et al.*, 1999). During the following years, Ronnblom *et al.* were able to show that these immune complexes may contain endogenous nuclear antigens bound to anti-dsDNA or snti-U1snRNP autoantibodies (Lovgren *et al.*, 2004). They act as potent ''self-antigens'' for TLR7 and TLR9 (Barrat *et al.*, 2005), and strongly induce type-I production of human pDCs *in vitro* (Marshak-Rothstein, 2006; see Figure 2). The source of DNA and RNA fragments in SLE patients is not yet identified, but recent studies showed that apoptotic or necrotic cells can generate interferonic DNA/RNA material (Lovgren *et al.*, 2004). Since SLE patients have a reduced clearance of dying cells, apoptotic RNA and DNA fragments are available in SLE patients *in vivo* (Herrmann *et al.*, 2000; Gaipl *et al.*, 2005).

During the last years it became evident, that the type-I IFN system also participates directly in the pathogenesis of CLE (reviewed by Wenzel and Tuting, 2007). The two major disease subtypes, chronic discoid LE and subacute cutaneous LE, typically show a histopathological ID pattern (Tebbe *et al.*, 1995). Patients with chronic discoid LE present with characteristic scarring erythematous macules and plaques, localized to the face or to the capillitium. Histologically a T-cell-rich ID affecting the junctional zone of the epidermis and the hair follicle is frequently observed. Cytotoxic lymphocytes infiltrate the dermo-epidermal zone and induce keratinocytic apoptosis (Figure 5; Wenzel *et al.*, 2005b). Patients with subacute cutaneous LE present with annular or

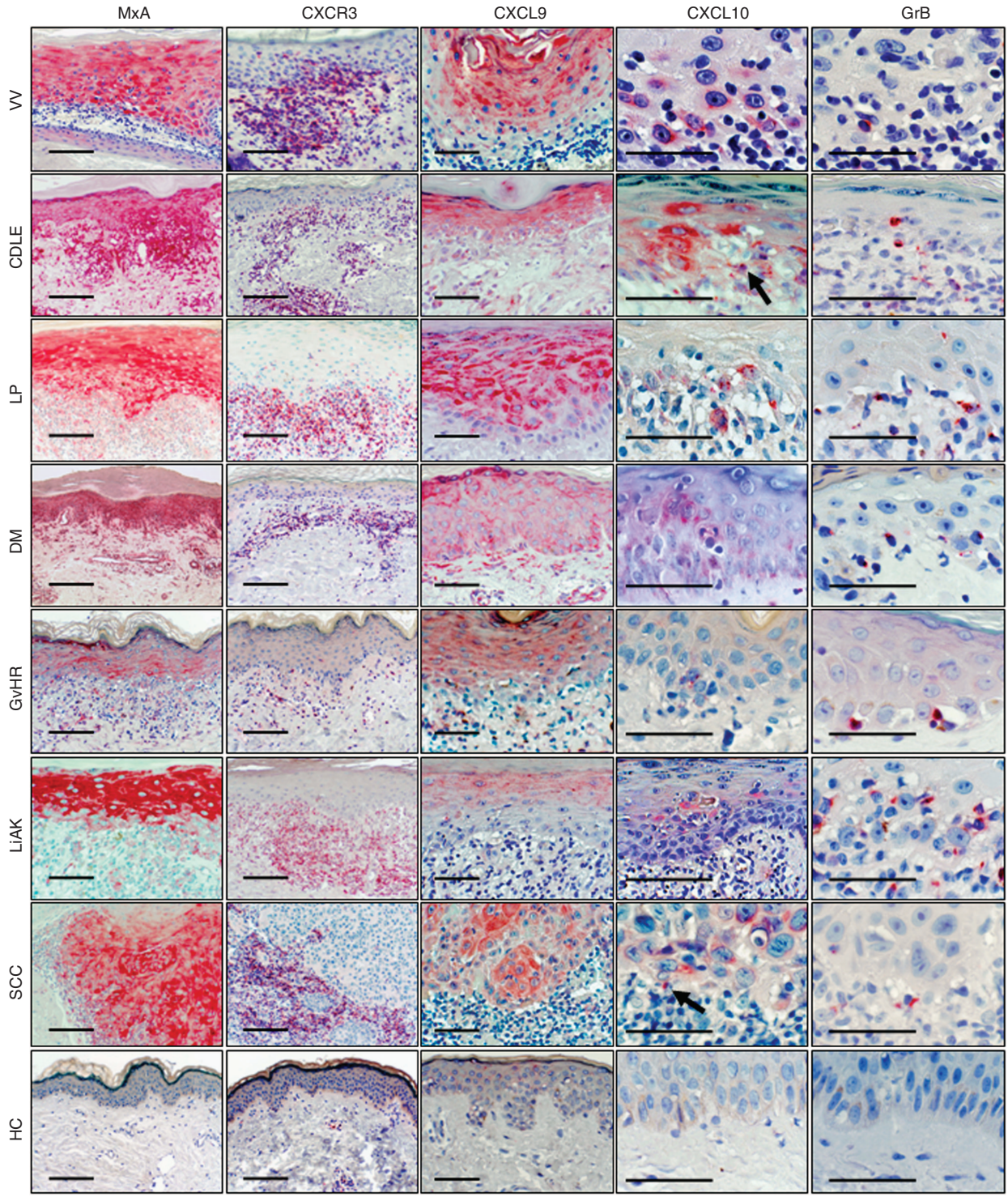

Figure 4. The type-I IFN-associated cytotoxic inflammation in different types of ID. A comparative overview of the IFN-associated inflammatory immune response found in different types of ID. A strong expression of type I IFN-inducible genes (MxA, CXCL9, CXCL10) is found in the epidermis and the upper dermis, whereas lymphoid cells expressing the corresponding chemokine receptor CXCR3 dominate the inflammatory infiltrate. Granzyme B-positive cytotoxic cells invade the epidermis and induce keratinocytic apoptosis in exactly those areas where the strongest CXCL10 expression is found. Some infiltrating lymphocytes carry CXCL10+ granules (arrow). As described in detail in this review, a similar inflammatory picture is found in several immune reactions that target epidermal viral, self-, or tumor antigens (LP, CLE, viral warts, non-melanoma skin cancer). However, it may also be found in other autoimmune disorders (for example, dermatomyositis, lichen sclerosus) as well as in several reactive conditions (drug reactions, graft-*versus*-host disease) that are accompanied by an ID pattern (Wenzel *et al.*, 2006b, 2007b; J Wenzel *et al.*, unpublished data). Bars = 100 μm. Abbreviations: VV, verruca vulgaris; CDLE, chronic discoid lupus erythematosus; LP, lichen planus; DM, dermatomyositis; GvHR, graft-*versus*-host reaction; LiAK, lichenoid actinic keratosis; SCC, squamous cell carcinoma; HC, healthy control.

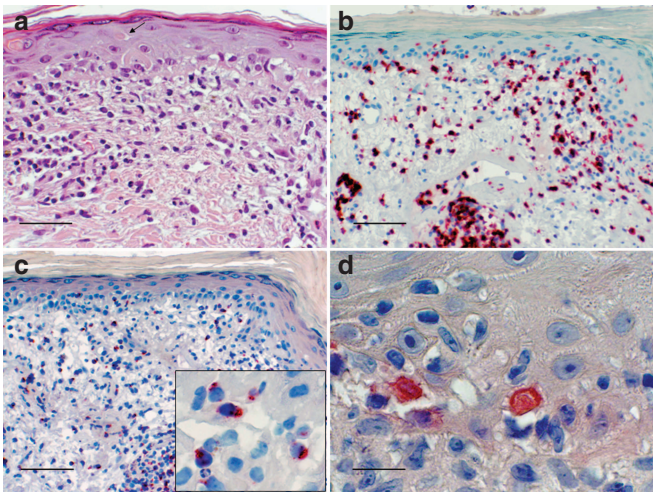

Figure 5. ID in CLE. The typical histological findings in chronic discoid CLE include a vacuolar degeneration of the basal epidermal layer with Civatte bodies (arrows) and infiltration of lymphoid cells (**a**). Dermal changes include a dense perivascular and peradnexal infiltration accompanied by mucin depositions. The lymphoid cells are mostly CD3 + T cells (**b**), which express cytotoxic markers such as Tia1 (**c**) and are accompanied by keratinocytic apoptosis in basal epidermal layers (**d**).

gyrate macules and plaques in sun-exposed areas, including shoulders, back, and arms. Lesional skin biopsies present histologically with a more cell-poor epidermal ID (Sontheimer, 2005). Antinuclear autoantibodies are found in 20–80% of CLE cases, depending on the underlying subtype (Wenzel *et al.*, 2000; Crowson and Magro, 2001). In particular, anti-SSA/Ro and anti-SSB/La antibodies are frequently found in CLE patients and associate closely with photosensitivity (Norris, 1993; Orteu *et al.*, 2001).

First evidence for a role of the type-I IFN system in CLE again came from clinical observations: Patients with widespread CLE skin lesions often present with flu-like symptoms, similar to SLE patients. These symptoms are associated with enhanced serum levels of the type-I IFN-inducible protein MxA, and upregulation of T-cell activation markers such as HLA-DR in peripheral blood (Wenzel *et al.*, 2005a, c). Large numbers of ''natural type-I IFN-producing'' pDCs are found in CLE-skin specimens (Blomberg *et al.*, 2001; Farkas *et al.*, 2001), accompanied by strong induction of the MxA protein and of the IFN-inducible chemokines CXCL9 and CXCL10, which mediate the recruitment CXCR3 + effector cells (Meller *et al.*, 2005; Wenzel *et al.*, 2005c; Wenzel and Tuting, 2007). Accordingly, the number of peripheral CXCR3 + T cells is significantly diminished in CLE patients with acute widespread skin lesions (Wenzel *et al.*, 2005c). The distribution of IFN-inducible proteins reflects the histological pattern that is typically seen in different CLE subtypes (Wenzel *et al.*, 2007c). Importantly, CXCL10 is expressed in exactly those epidermal areas where CTLs invade the basal layer, suggesting a role of this chemokine in the typical ID pattern (depicted in Figure 4). Some infiltrating lymphocytes carry CXCL10-positive granules (Wenzel and Tuting, 2007; Wenzel *et al.*, 2007c).

The primary mechanisms of IFN induction in CLE are still unclear, but TLR activation by immune complexes, similar to SLE, might play a role. Apoptotic cells accumulate in the skin of patients with CLE after UV irradiation, probably as a result of impaired or delayed clearance (Kuhn *et al.*, 2006). This is supported by recent observations from autoimmune, non-obese diabetic mice that demonstrated an increase in apoptotic cell load following UV-light exposure to keratinocytes when compared with control strains (O'Brien *et al.*, 2006). The non-engulfed cells may undergo secondary necrosis and release proinflammatory compounds and potential autoantigens, which may support the formation of skin lesions in this disease (Kuhn *et al.*, 2006). Additionally, a DNA-damage response induced by UV light might be involved.

Recently, we developed a hypothetical model for a vicious proinflammatory circle in CLE: a primary, still unknown, stimulus induces the lesional expression of type-I IFNs and of proinflammatory, IFN-dependent cytokines, including CXCL9 and 10. Earlier observations suggest that UV light might play a pivotal, initiating, role (Norris, 1993; Sontheimer, 1996). Subsequently, the activated IFN-system drives the recruitment of CXCR3 + effector lymphocytes and pDCs into the skin. At least three different self-perpetuating mechanisms could be envisioned, which may support the chronic inflammation seen in CLE: (i) some infiltrating lymphocytes carry CXCL10 in their granules, which is released together with the cytotoxic proteins, and might support a direct ''lymphocyte self-recruitment'', (ii) recruitment of CXCR3 + pDCs augments production of lesional type I IFNs, which again perpetuates the lesional inflammation, and (iii) the cytotoxic lesional inflammation leads to cell destruction and impaired apoptosis, which again induces expression of several proinflammatory mediators and the release of nuclear fragments. This drives the lesional inflammation, especially in the basal epidermal areas with CTL invasion, and may, in part, be responsible for the ID pattern seen in CLE (Wenzel and Tuting, 2007).

PRESENCE OF A HISTOLOGICAL ID PATTERN IN (PRE-) MALIGNANT KERATINOCYTIC NEOPLASMS

A histological ID pattern is also frequently seen in (pre-) malignant keratinocytic neoplasms of the skin such as actinic keratosis (AK) and squamous cell carcinoma (SCC). AK is the most frequently occurring form of ''carcinoma *in situ*'' that is commonly seen in sun-damaged skin. Left untreated, this condition has an approximate risk of up to 10% risk for transition into invasive SCC. AK presents histologically with atypical keratinocytes and a disordered epidermal structure, as well as with solar elastosis in the dermis. UV-induced mutations of the p53 tumor-suppressor gene are found in the majority of AKs and appear to play a central pathogenetic role in AKs and SCCs (Nomura *et al.*, 1997). Inflammatory changes, including a vacuolar degeneration of the basal cell layer with some keratinocytes and a band like T-cellular inflammatory infiltrate, are often seen in AKs. These lesions are termed ''lichenoid'' AK, due to the histological similarities with LP (Prieto *et al.*, 1993; Hussein and Ahmed, 2005).

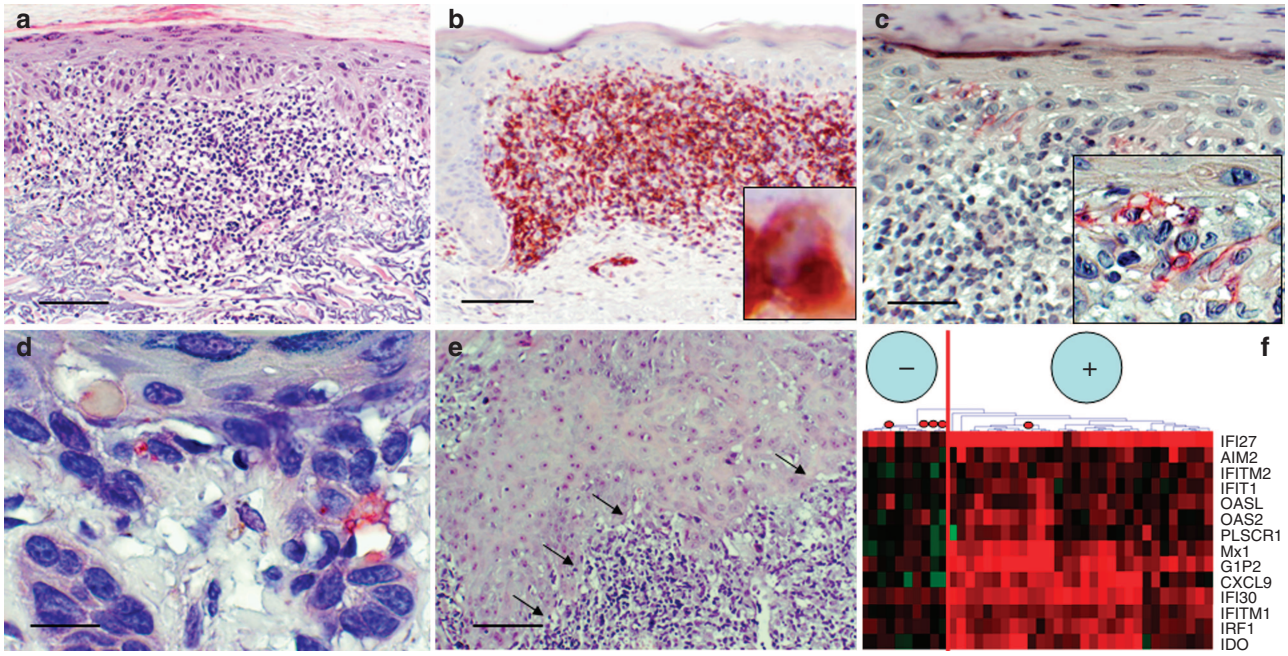

Figure 6. Type I IFN associated junctional inflammation in non-melanoma skin cancer. LAK is regarded to reflect an immunological reaction against malignant transformed keratinocytes. Here, a dense band-like ''lichenoid'' inflammatory infiltrate consisting of cytotoxic CXCR3 + lymphocytes is typically seen (**a**, hematoxylin–eosin; **b**, CXCR3 (brown) and granzyme B (red) co-staining). Numerous CD123 + pDCs are found along the dermo-epidermal junction (**c**). Keratinocytic apoptosis (demonstrated by caspase 3 staining) in areas where lymphocytes invade the epidermal layer (**d**). Note the disordered structure and the nuclear atypia of the epidermis, which are typically seen in AK. An ID-like pattern (**e**, hematoxylin–eosin) and an IFN-associated inflammation (**f**) may also be present in invasive SCC. Results of a gene-expression analysis in 40 SCC samples, followed by unclassified clustering (**f**). Here, two distinct SCC subsets were identified, one with a strong expression of IFN-inducible genes (+) and one without (−) them. Interestingly, almost all SCC patients who received long-term immunosuppression due to organ transplantation (red points) clustered into the IFN (−) group. (The expression ratio (**f**) ranges from threefold downregulated (green) to threefold upregulated (red).) Bars = 100 μm (**a**, **b**, **c**, **e**) or 500 μm (**d**).

The lichenoid inflammation pattern is regarded to reflect an immunological reaction against malignant transformed keratinocytes (Tan and Marks, 1982). This assumption is supported by the fact that AK has a great tendency for spontaneous regression (Marks, 1986). The frequency of AK is increased in immune-suppressed patients, demonstrating the role of a functional immune system (Ulrich *et al.*, 2003). CD3 + T-lymphocytes, including numerous Tia1 + cytotoxic T cells, dominate the mononuclear infiltrate in inflammatory AK (Hussein and Ahmed, 2005). Similar findings were also made in invasive SCCs. Here, an ID-like histological pattern may be seen at the tumor invasion front, making it difficult to distinguish initial SCC from CLE in some cases (Kurihara and Hashimoto, 1985; Zedek *et al.*, 2007). Cytotoxic T cells infiltrating SCCs have been shown to specifically recognize mutated epitopes of p53 involved in keratinocyte transformation, supporting a role of this immune response in tumor control (Black and Ogg, 2003). As depicted in Figure 4, the lichenoid inflammation in AK may be accompanied by a similar immunohistochemical-pattern as seen in autoimmune IDs. Strong expression of MxA and CXCL9 is found in the epidermis and within the inflammatory infiltrate. Recruitment of pDCs and CXCR3 + cytotoxic lymphoid cells, as well as CXCL10 expression, is detectable in exactly those areas with hydropic degeneration of the basal epidermis. Numerous CD123 + pDCs are found at the dermo-epidermal junction, and CXCR3 + cytotoxic effector cells infiltrate the epithelium in areas where keratinocytes undergo apoptosis (Figure 6). A similar expression pattern of IFN-inducible proteins is also found in several SCC specimens (Figure 4). Gene-expression analyses of SCCs show upregulation of numerous IFN-associated genes (Mx1/MxA, IRF1, IFI30, CXCL9). This list of IFN-associated genes in SCCs (depicted in Figure 6f) agrees largely with the ''IFN signature'' originally described in SLE patients (Baechler *et al.*, 2003; Bennett *et al.*, 2003; J Wenzel *et al.*, unpublished data). Interestingly, this IFN signature was almost absent in organ-transplant recipients under immunosuppressive therapy, who have a significantly poorer clinical prognosis (Figure 7).

TYPE-I IFNS AND TUMOR IMMUNOSURVEILLANCE IN THE SKIN

Burnet (1970) already hypothesized in 1970 that the immune system is able to detect and eliminate transformed cells. This ''immunosurveillance hypothesis'' has been controversially debated for many years (Dunn *et al.*, 2004). Clinical observations directly support a role for the immune system in tumor growth control, since the incidence of skin cancer is significantly enhanced in organ-transplant recipients under long-term immunosuppression (Alam and Ratner, 2001; Ulrich *et al.*, 2003). Direct evidence that the type-I IFN system participates in tumor immunosurveillance came from experiments with genetically engineered mice that lacked genes coding for IFN receptors or IFN-signaling molecules.

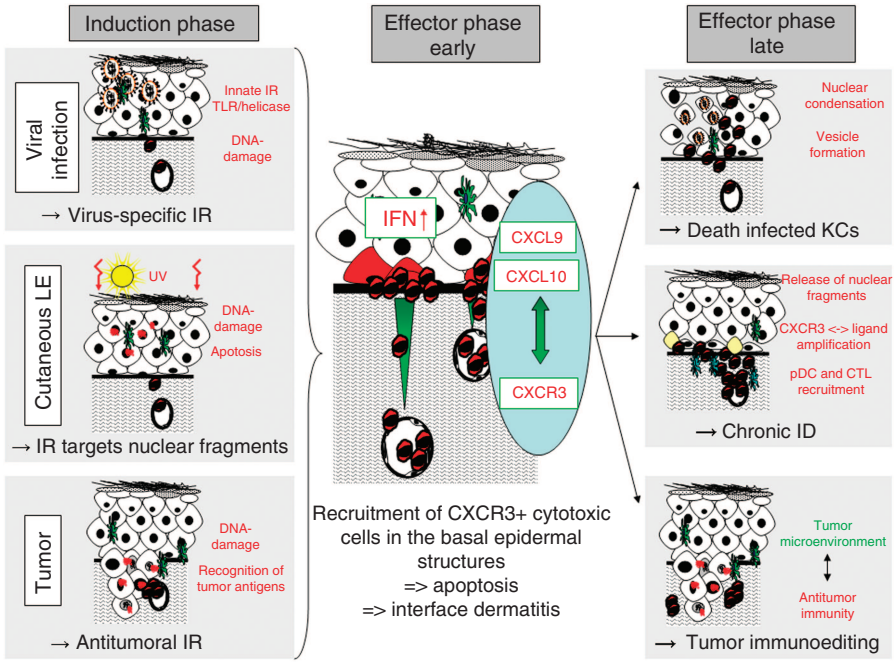

Figure 7. The common pathogenetic mechanisms for a type-I IFN-associated cytotoxic inflammation in viral infection, autoimmune disease, and antitumor immunity. This model depicts the common mechanisms involved in antiviral, autoimmune, and antitumor immune reactions. In the case of a viral infection of keratinocytes, cutaneous DCs become activated by the initial innate immune response in the induction phase. DCs then migrate to the regional lymph node and induce a virus-specific T cellular immune response. In autoimmune conditions, such as LP and CLE, infiltrating lymphocytes are supposed to recognize keratinocytic autoantigens and nuclear fragments. In non-melanoma skin cancer, CTLs have been shown to recognize mutated epitopes of p53 involved in keratinocyte transformation. Independently from these etiopathogenetic differences, a similar ID-like pattern due to cytotoxic lymphocytes that infiltrate the basal epidermal layers and induce keratinocytic apoptosis may be seen in all these diseases in the early effector phase. In older lesions, during the late effector phase, the characteristic histopathological differences between these conditions are found. Viral lesions show the typical acantholytic, intra-epidermal vesicles. CLE presents with a chronic ID. In non-melanoma skin cancers, the mechanism of tumor immunosurveillance and tumor immunoediting evolve their impact (review by Dunn *et al.*, 2006).

These mice not only succumb to viral infections, but are also more prone to develop carcinogen-induced epithelial or mesenchymal tumors (Shankaran *et al.*, 2001; Dunn *et al.*, 2005). DNA damage, which is associated with neoplastic cellular transformation, has been suggested to play a significant role in IFN induction in tumors (Xu, 2006). The DNA-damage response activates innate immunity via stimulation of IRF1 and IRF3, which both induce the expression of type-I IFNs (Taniguchi *et al.*, 2001; Barnes *et al.*, 2002). Additionally, DNA damage is associated with enhanced expression of ligands, which are involved in the activation of natural killer- and CD8+ T-cells during infection or neoplastic transformation (Gasser *et al.*, 2005; Xu, 2006). The IFN-associated inflammatory reaction, leading to the ID pattern in LAK and SCC, appears to reflect a cellular tumor-antigen-specific immune response targeting the basal epidermal areas in LAK and the invasive tumor cells in some SCCs (J Wenzel *et al.*, unpublished data).

AN IFN-ASSOCIATED CYTOTOXIC CELLULAR IMMUNE RESPONSE AGAINST VIRAL, SELF-, OR TUMOR ANTIGENS IS A COMMON PATHOGENETIC FEATURE IN "ID"

The histological "ID" pattern is found in a large spectrum of skin diseases, including autoimmune, infectious, reactive, and neoplastic disorders. We propose that this pattern morphologically reflects a cytotoxic cellular immune response against keratinocytes, which is associated with activation of the type-I IFN system. In viral skin infections, CTLs recognize viral antigens presented by infected keratinocytes via major histocompatibility-I (Mikloska *et al.*, 1996). Consequently, an ID pattern may be seen in early HSV lesions, whereas older lesions show acantholytic, intra-epidermal vesicles (Huff *et al.*, 1981). In cutaneous autoimmune diseases, keratinocytic autoantigens may play a pivotal role: "autocytotoxic" CD8+ T cells recognizing keratinocyte antigens have been identified in LP (Sugerman *et al.*, 2000). In cutaneous lupus erythematosus, immune complexes comprising antinuclear antibodies and nuclear antigens, which are released after UV-light exposure, may stimulate IFN pathways and support lesional inflammation. This stimulation probably depends on TLR-mediated recognition of endogenous nucleic acids in the endosome of specialized immune cells, since chloroquine (which blocks endosomal acidification) is an effective drug for this disease (Rutz *et al.*, 2004). Additionally, CTLs recognizing epidermal autoantigens might play a role in some CLE subsets (Wenzel and Tuting, 2007). Interestingly, an activated IFN system appears also to be involved in the pathogenesis psoriasis (Boyman *et al.*, 2004; Lande *et al.*, 2007). However, this disease does not typically present with ID, and here lymphocyte recruitment via CXCR3↔ligand interaction

appears to be less relevant than in CLE or LP (Wenzel *et al*., 2008).

An ID-like pattern may also be found in LAK and in SCC. Here, neoplastic transformed keratinocytes are probably the main target of the immune cells and CTLs may specifically recognize tumor-specific antigens such as mutated epitopes of p53 (Black and Ogg, 2003).

Taken together, we show that skin disorders, which are histologically characterized by an ID pattern, share a common immunohistological picture, with epidermal expression of the IFN-inducible proteins MxA, CXCL9, and CXCL10 accompanied by infiltrating CXCR3+ cytotoxic lymphoid cells. In all investigated ID conditions, independent from the different pathogenetic background, CXCL10 is expressed in exactly those areas where CXCR3+ CTLs infiltrate the basal epidermis and induce keratinocytic apoptosis. Gene-expression analyses revealing a lesional ''IFN signature'' support the role of type-I IFNs in these conditions.

These data indicate that the common molecular and cellular basis underlying the morphological picture of ID is an IFN-associated cytotoxic attack against the basal keratinocyte layers.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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